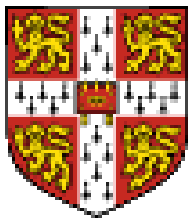
Sex Chromosome Structure and Function Part II 2015/16



University of
CAMBRIDGE
Department of Pathology

Dr Peter Ellis
University of Kent

Lecture 1: Structural considerations

- Definition of sex chromosomes
  - Sex determining genes as a “switch” within a network
- X / Y heteromorphism: gross differences between X and Y
  - Reasons for Y degeneration
  - Reasons for X conservation
- Consequences of X / Y heteromorphism: dosage compensation
- Pathologies involving gross sex chromosomal abnormality
  - Aneuploidies
  - Defects involving X inactivation

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What are sex chromosomes?

Sex chromosomes (or gonosomes) are chromosomes whose complement differs between male and female.

What are sex chromosomes?

Since the chromosome complement varies between the sexes, they come under different selective pressures, which shape their structure, transcriptional activity and gene content, leading to functional specialisation.

There are many different types of sex chromosome arrangement, implying that sex chromosomes have evolved independently multiple times.

Many species do not have sex chromsomes: e.g. sex in reptiles is dependent on the incubation temperature of the eggs. Environmental sex determination (or hermaphoditism / cosexuality) is the ancestral state from which sex chromosome systems evolve.

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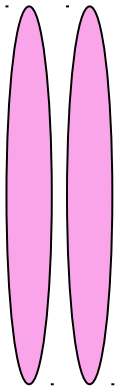

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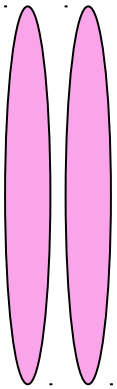

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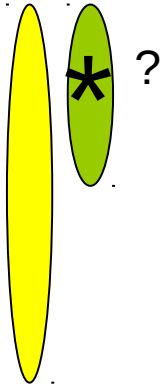


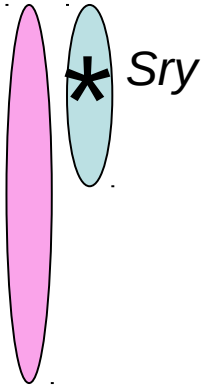
ZW

Male heterogamety
* specifies maleness
e.g. mammals

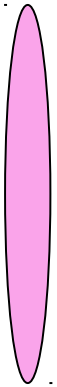
Dosage based
e.g. *C. elegans*

Female heterogamety.
Dosage or dominant W gene. Birds: one factor is dosage of *Dmrt1*)

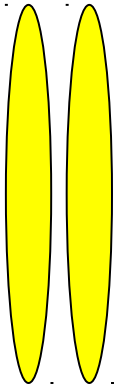
♂



XY



XO



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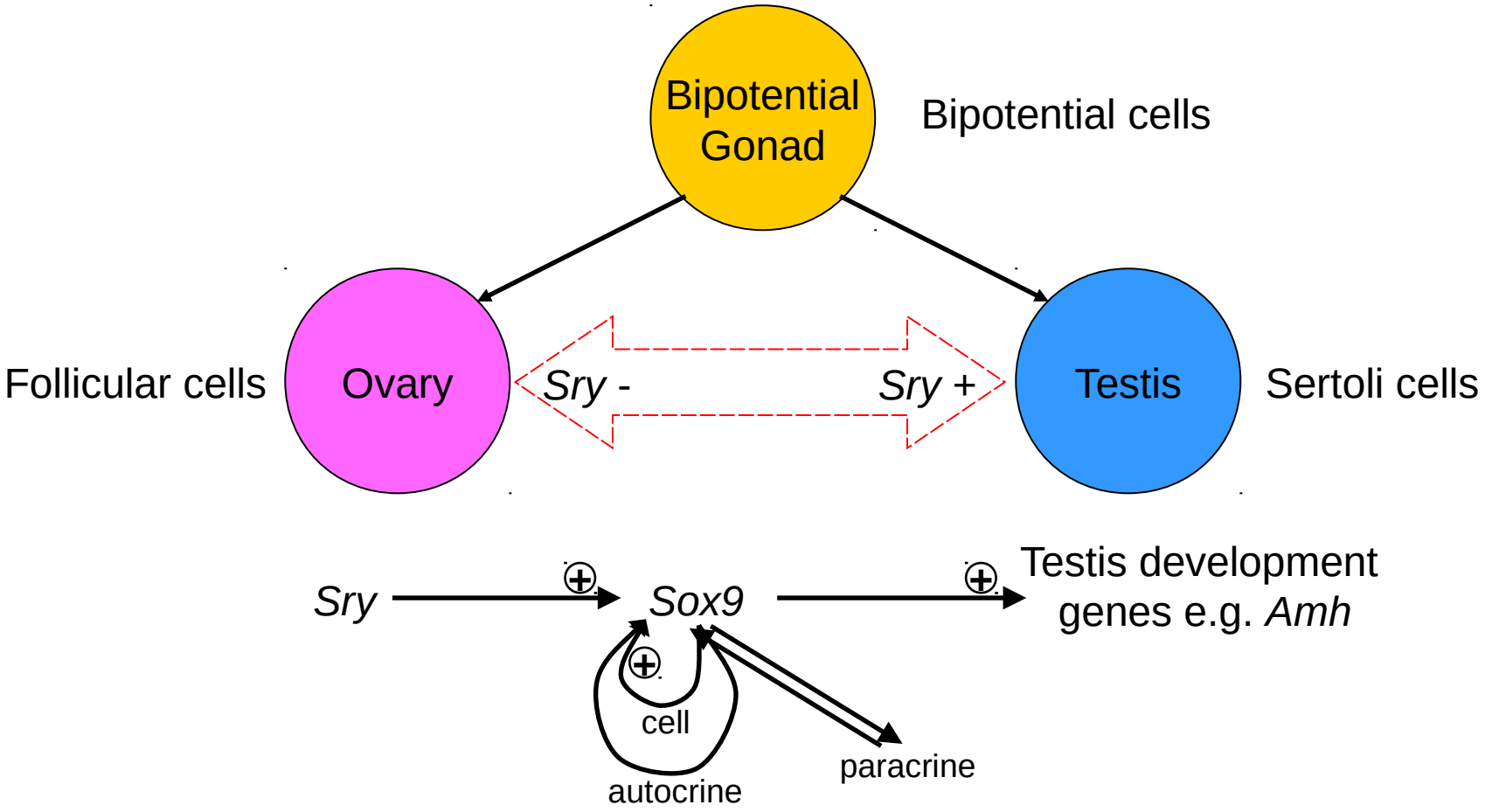
Key point: The ovary / testis differentiation pathway is conserved across all vertebrates, only the switching mechanism is different.

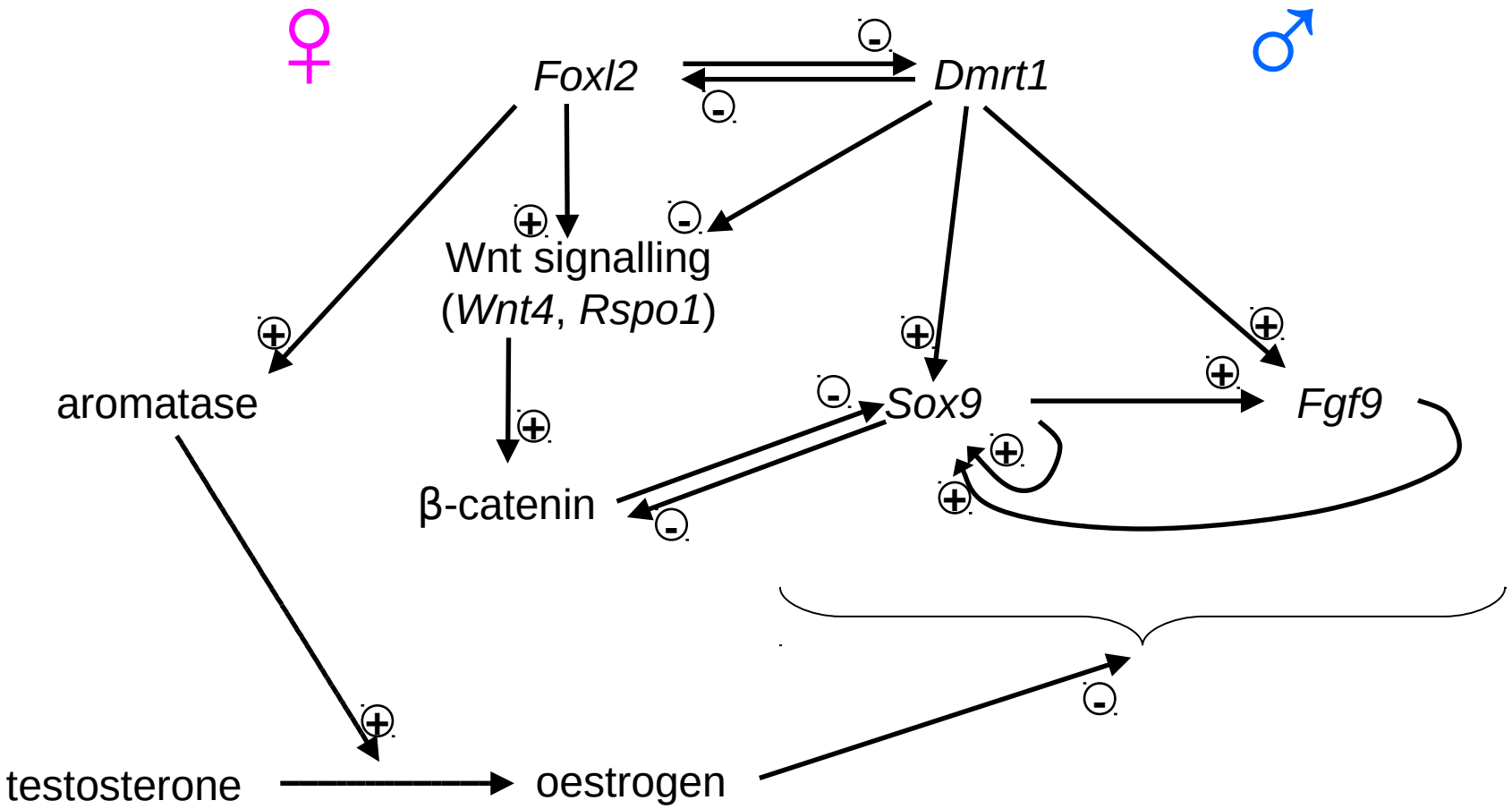
Sertoli cell fate choice: (gonadal) sex determination



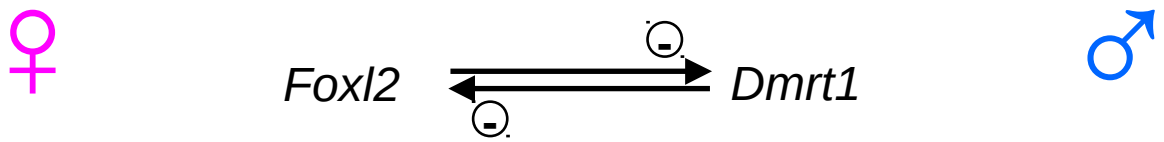
Positive feedback reinforcement creates a switch
Once differentiation has started it is “locked in”

3 levels: self-activation within the cell, autocrine effects via *Fgf9 / Fgfr*, paracrine effects on adjacent cells via prostaglandin D2

Choice between male and female “modules”



Choice between male and female "modules"



Ancestral vertebrate sex determining system appears to involve choice between two gene networks centred on *Foxl2* (ovary-determining) and *Dmrt1* (testis-determining), perhaps governed by environmental factors such as temperature.

Numerous different genetic "switches" have evolved in different lineages:

Dmy (dominant male gene, Medaka Y)
DM-W (dominant female gene, Xenopus W) – likely a dominant negative mutant
Dmrt1b (dose sensitive male gene, chicken Z)
Sry (dominant male gene in mammals – short circuit that activates downstream genes)

* *Dmrt1* and *Foxl2* are important to *maintain* male/female identity in mammalian cells

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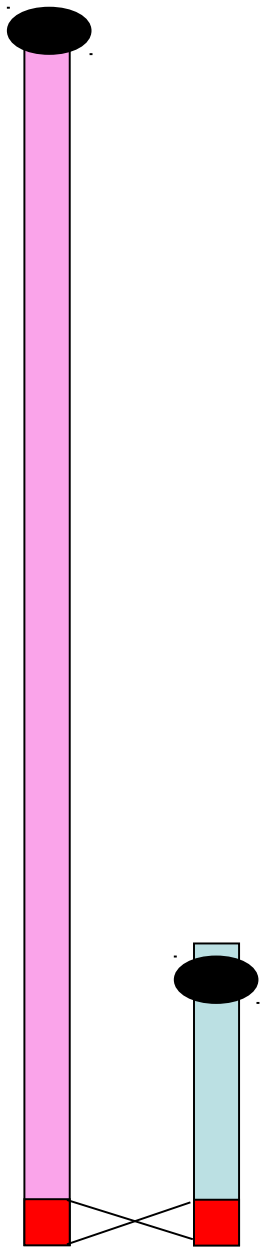
Mammalian sex chromosomes are heteromorphic (non-identical in size, sequence and structure), and most of their length does not undergo crossover / recombination during meiosis.

Small regions of identity are retained and undergo obligatory recombination and exchange at meiosis. This crossover is necessary pass cell cycle checkpoints and ensure correct segregation of homologs.



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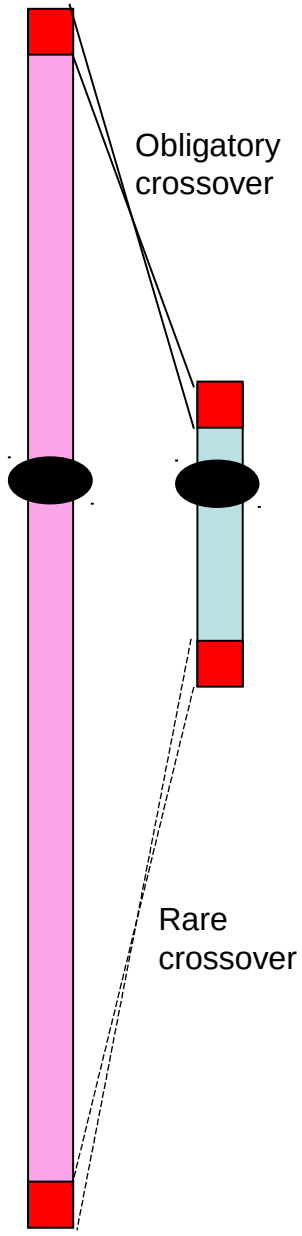
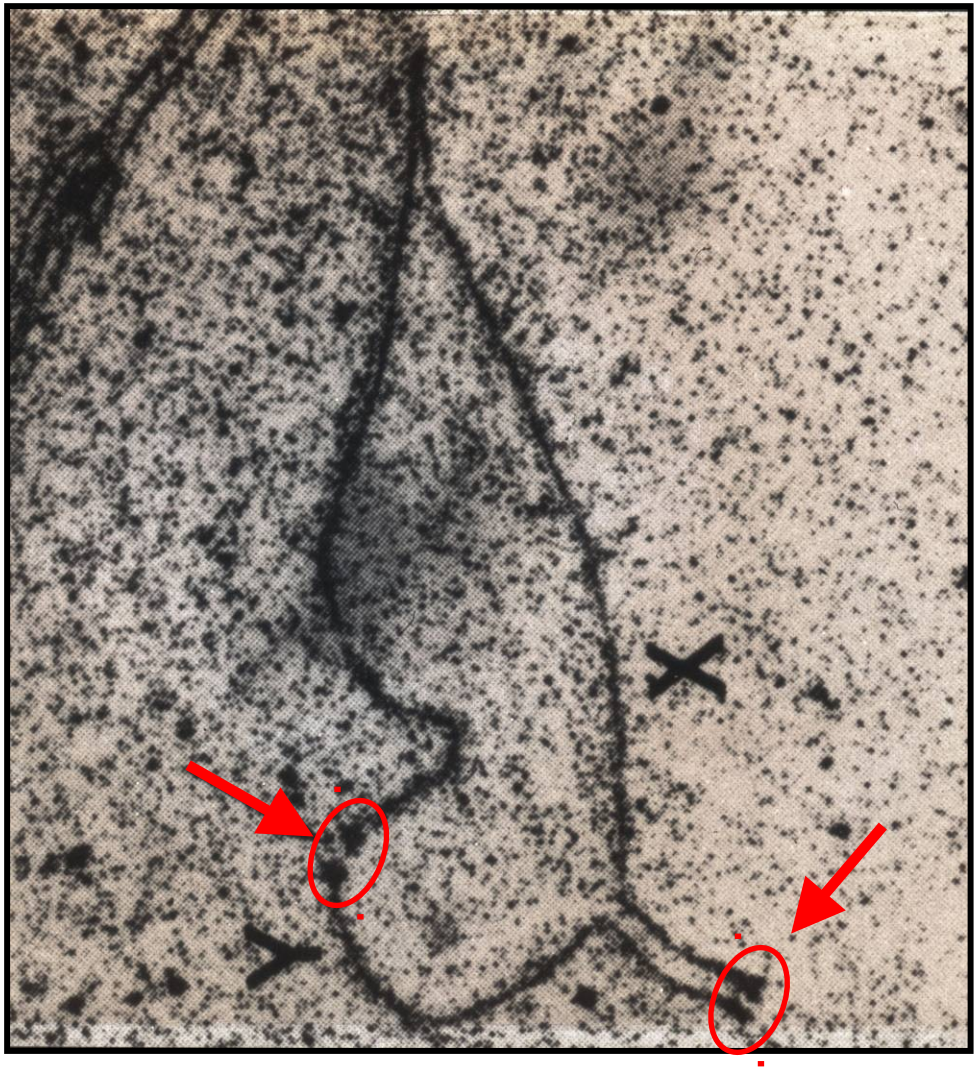


Human



Electron micrograph of XY pairing during meiosis

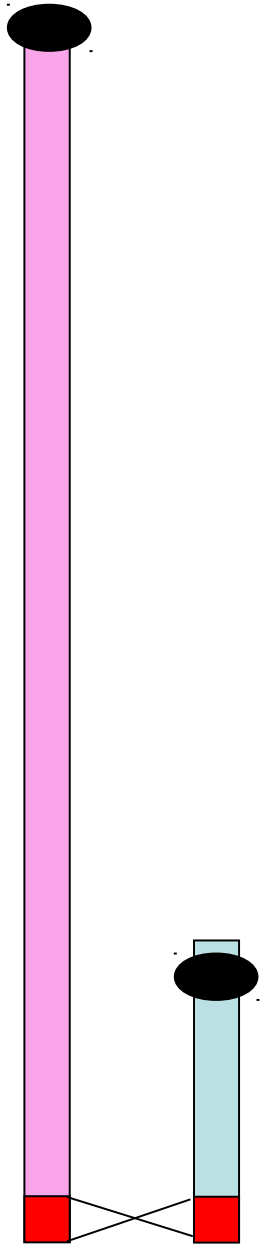
The X chromosome is large and comparatively gene-rich, while the Y chromosome is small, degenerate and comparatively gene-poor.

X chromosome gene content is largely conserved across mammalian species, while Y chromosome gene content is highly variable.

Both chromosomes are enriched for repeat sequences such as LINE elements and endogenous retroviruses (Y much more so than X).

Both chromosomes also have a high rate of segmental duplication, in particular amplified gene families, some of which are in large inverted repeats / palindromes.

Why is this?



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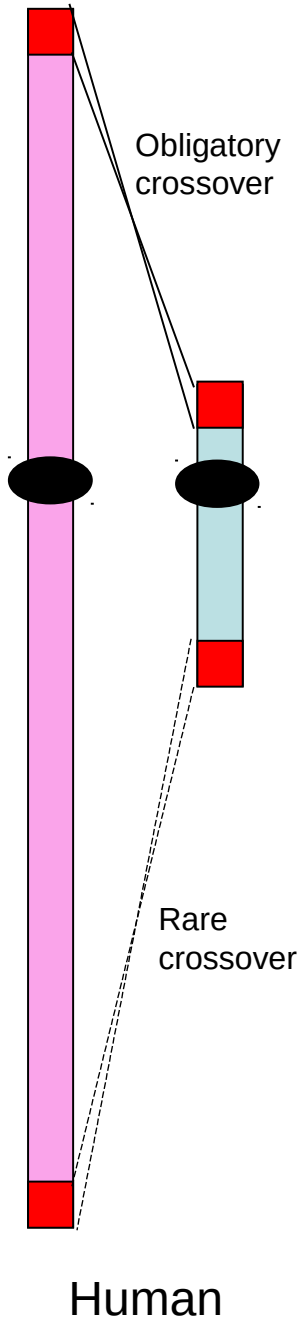

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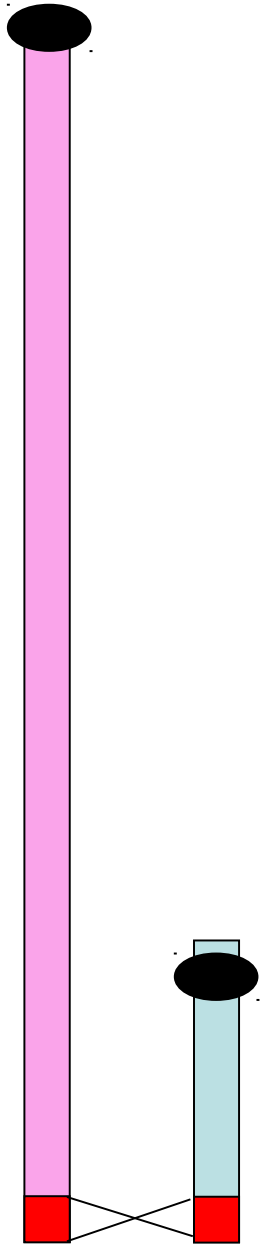

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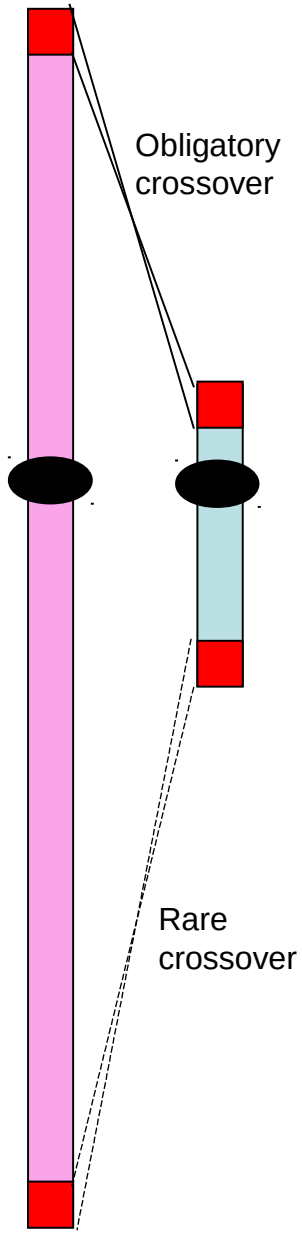


Human

Explaining sex chromosome heteromorphism

The size difference arises due to degeneration of the Y chromosome.

Two key factors:

- Reduced population size: quarter the copy number relative to autosomes
  Smaller population increases the fixation rate for slightly deleterious mutation as selection is less efficient
- All genes within the non-recombining region are linked

Explaining Y chromosome degeneration

Four statistical models:

1)	Muller's Ratchet	*Stochastic loss of the Y chromosome haplotype with the lowest mutational load*
2)	Background selection	*Newly-arising weakly beneficial mutations cannot "escape" from the haplotype they arose on and may be lost if that background has a high mutational load*
3)	Hitch-hiking	*A strongly-selected beneficial mutation can drag many other weakly deleterious mutations to fixation*
4)	Hill-Robertson effects with weak selection	*A generalisation of models (2) and (3) to cover the effects of many mutations with weak positive or negative effects, plus other factors such as back mutation*

So, why have sex chromosomes at all?

Many species don't! Evolution of a sex chromosome pair requires two factors:

1) Environmental sex determination (the ancestral state) becomes superseded by a dominant sex-determining allele.

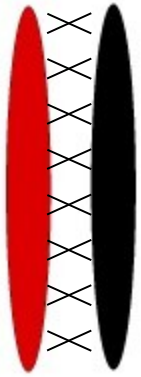
May simply be a random event or may be a response to environmental change

2) Recombination between the incipient sex chromosomes becomes suppressed in the region around the sex-determining allele.

Arises in order to preserve a favourable gene combination, e.g. linkage between a gene promoting sperm formation and a male-determining gene. Chromosomal inversions are frequently a factor.

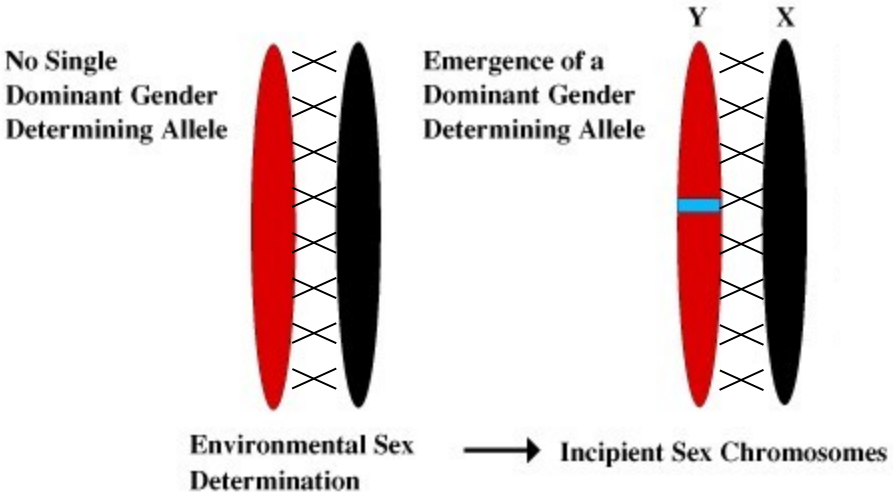
Simple Model of Mammalian Sex Chromosome Evolution

No Single
Dominant Gender
Determining Allele



Environmental Sex
Determination

Simple Model of Mammalian Sex Chromosome Evolution



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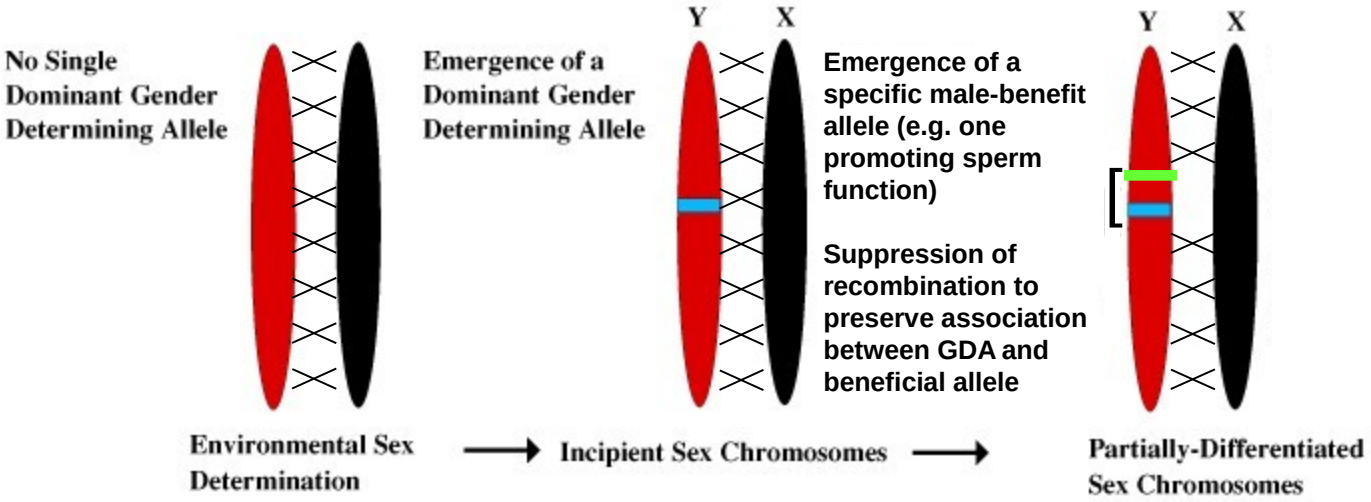

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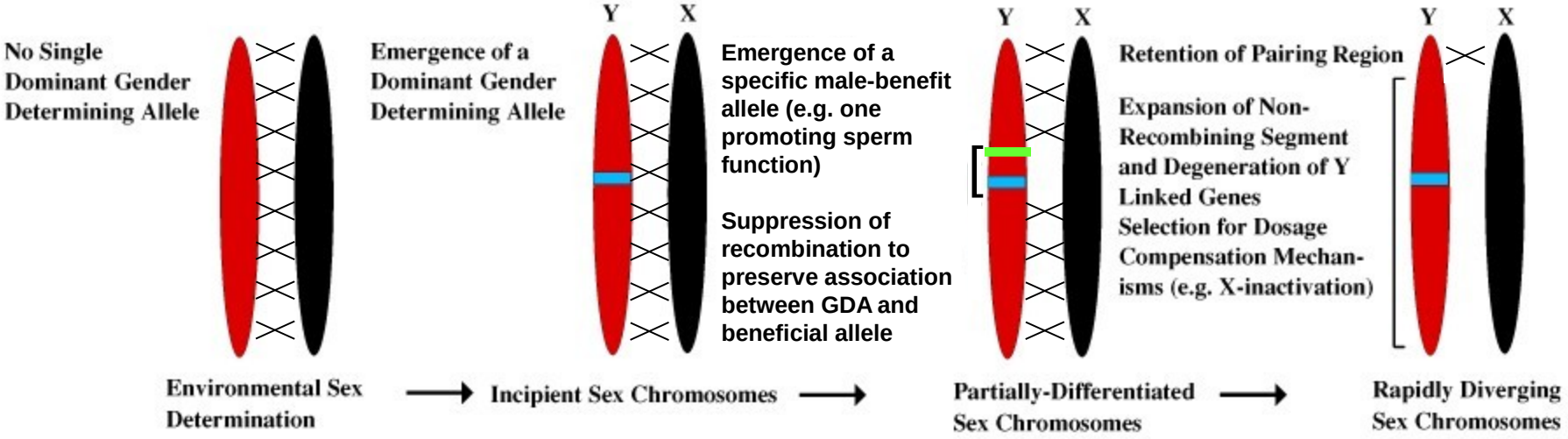


Stages of Y chromosome degeneration

Y chromosomes in differing stages of degeneration can be observed in various species:

- *Medaka* (fish) – newly forming sex chromosome system. PAR comprises most of the length of the sex chromosomes. The non-pairing segment is restricted to a small region around the sex-determining gene. Gene loss and retrovirus accumulation already under way.
- Mammals – well-established sex chromosome system, Y is highly degenerate and much smaller than the X.

General principle: Y chromosomes degenerate over evolutionary time and lose function.

- *Drosophila miranda* – fruit flies in general have a long-established highly heteromorphic sex chromosome pair. However, a new segment has recently been added to the Y and degeneration is incomplete.

Why doesn't the Y chromosome disappear?

Retention of important genes

Sufficiently strongly-selected genes will remain active on the Y chromosome despite the evolutionary forces driving Y degeneration. Two types of genes are retained on the Y.

1) Genes with a direct benefit to males – these are naturally strongly selected for

2) Housekeeping genes where dosage is critical – in this case loss of the Y copy is strongly selected against

Why doesn't the Y chromosome disappear?

Acquisition of new Y content (may subsequently become amplified)

- Direct transposition from the X chromosome
  (e.g. *Tgif2ly* and *Pcdh11y* , a human-specific X-to-Y transposition)
- Direct transposition from autosome
  (e.g. *Daz*, a primate-specific autosome-to-Y transposition)
- Via the PAR
  (Several additions in the course of mammalian evolution)

Why doesn't the Y chromosome disappear?

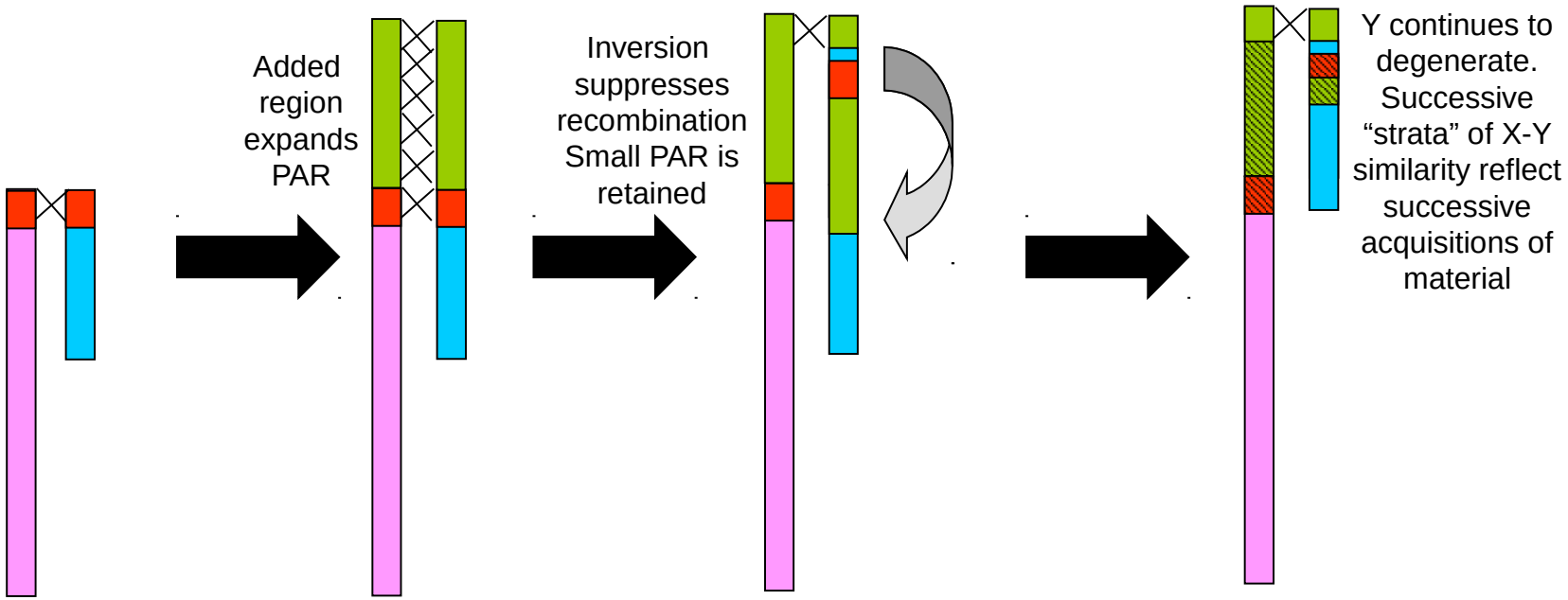
Amplification of key Y genes by unequal sister chromatid exchange

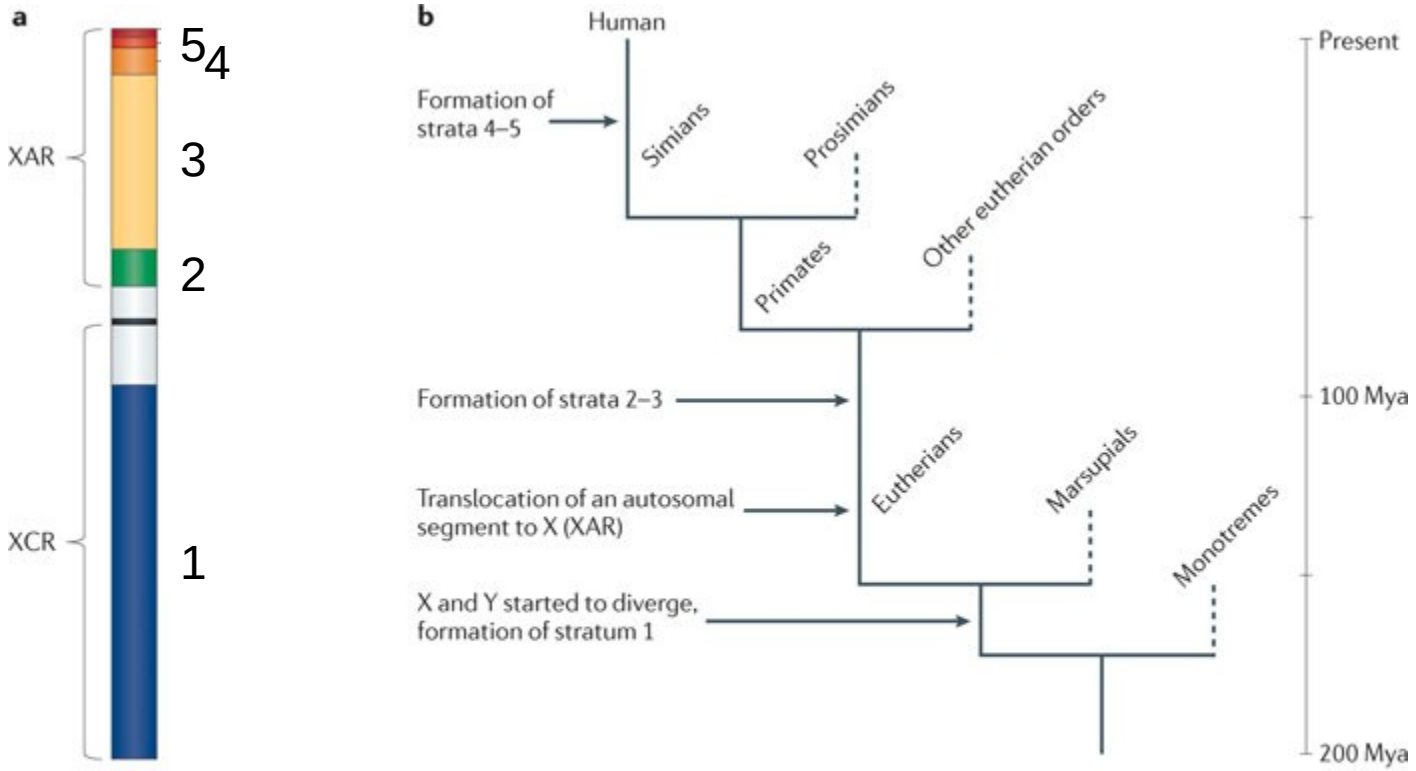
Amplification serves several purposes:

- Provides "back-up" copies of key genes so that function is not lost if a single copy becomes mutated
- May allow for intra-chromosomal pairing and gene conversion, "repairing" damaged gene copies.
  Note: this suggestion is controversial as gene conversion is not directional. Any given conversion event is as likely to destroy a functional copy as to repair a damaged copy.
- Direct "selfish" benefit in cases of genomic conflict (sex ratio distorters)

Acquisition through the PAR

- Translocation of an autosomal region into the PAR
  Expands the pairing region between the X and Y chromosomes
- Expansion of the non-recombining region via sequence rearrangement which suppresses recombination across part of the enlarged PAR
  Once again, this is likely to occur in order to retain male-benefit alleles on the Y chromosome
- Subsequent degeneration of the Y copy of the sequence, with only male-benefit genes being retained





(from *Ellegren H.* **Nat Rev Genet.** 2011 Mar;12(3):157-66)

The mammalian sex chromosomes have grown by additions through the PAR. These strata are revealed by comparison of the X and Y sequences. The Y has lost most of the gene content of each stratum. There are five major strata on the human X

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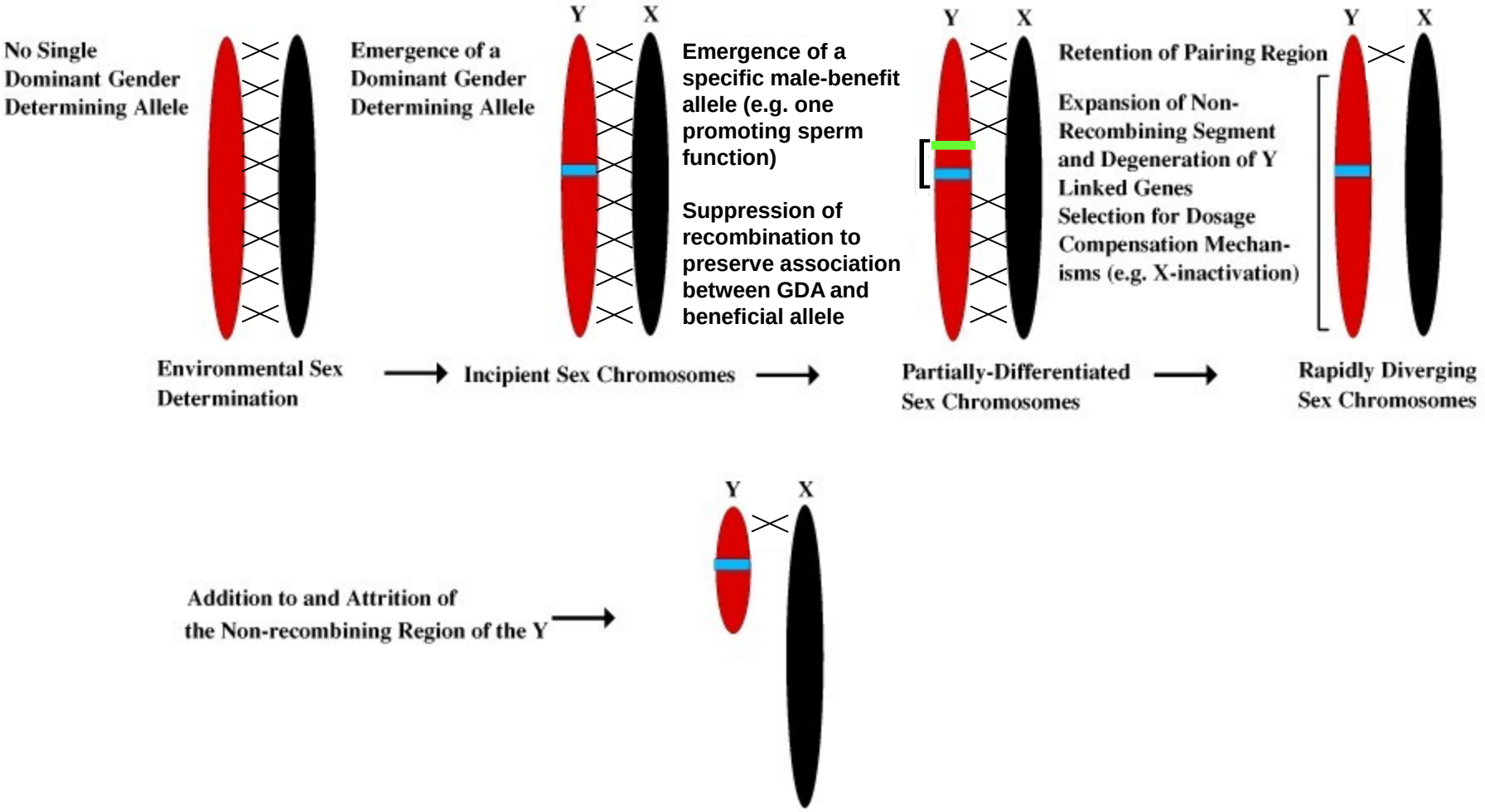

Y chromosomes in different lineages retain different genes

	Catarrhine primates			Carnivores		Rodents
	Rhesus	Chimp	Human	Dog	Cat	Mouse
Stratum 1						
SRY	A	A	A	A^D	A	A
HSFY	A^D	L	A^D	A	A^D	L
RBMY	A	A	A	A	L	A^D
CUL4BY	L	L	L	A^D	A^D	L
RPS4Y	A^D	A^D	A^D	L	A^D	L
TSPY	A^D	A^D	A^D	A^D	A^D	ψ
Stratum 2/3[a]						
KDM5C	A	A	A	A	A	A
UBE1Y	ψ	ψ	ψ	A	A	A
UTY	A	A	A	A	A	A
DDX3Y	A	A	A	A	A	A
USP9Y	A	ψ	A	A	A	A
BCORY	ψ	ψ	ψ	A^D	L	L
ZFY	A	A	A	A	A	A^D
EIF2S3Y	L	L	L	A^b	A	A
EIF1AY	A	A	A	A	A	L
CYorf15	A^D	A	A^D	A	A^D	L
Stratum 4						
AMELY	A	A	A	L	A	L
TOTAL RETAINED Ancestor ($n = 17$)[c]	14	12	13	15	15	9

(from *Li G et al.* **Genome Res.** 2013 Sep;23(9):1486-95.

Classes of sequence on the Y

- **PAR**
  100% sequence identity between X and Y, recombines at meiosis
- **X-transposed**
  Very high sequence identity between X and Y, reflects recent direct X –to-Y transfer of sequence
- **X-degenerate**
  Genes that were present on the ancestral autosomes, or which have been acquired through the PAR. Degree of X-Y similarity reflects the age of incorporation into the non-recombining region. Four strata on the primate sex chromosomes (plus X-transposed in humans makes five):

  1) Ancestral
  2) Present in marsupials and eutherians only
  3) Present in eutherians only
  4) Primate-specific

- **Ampliconic**
  Amplified on the Y. May or may not have an X or autosomal homologue.

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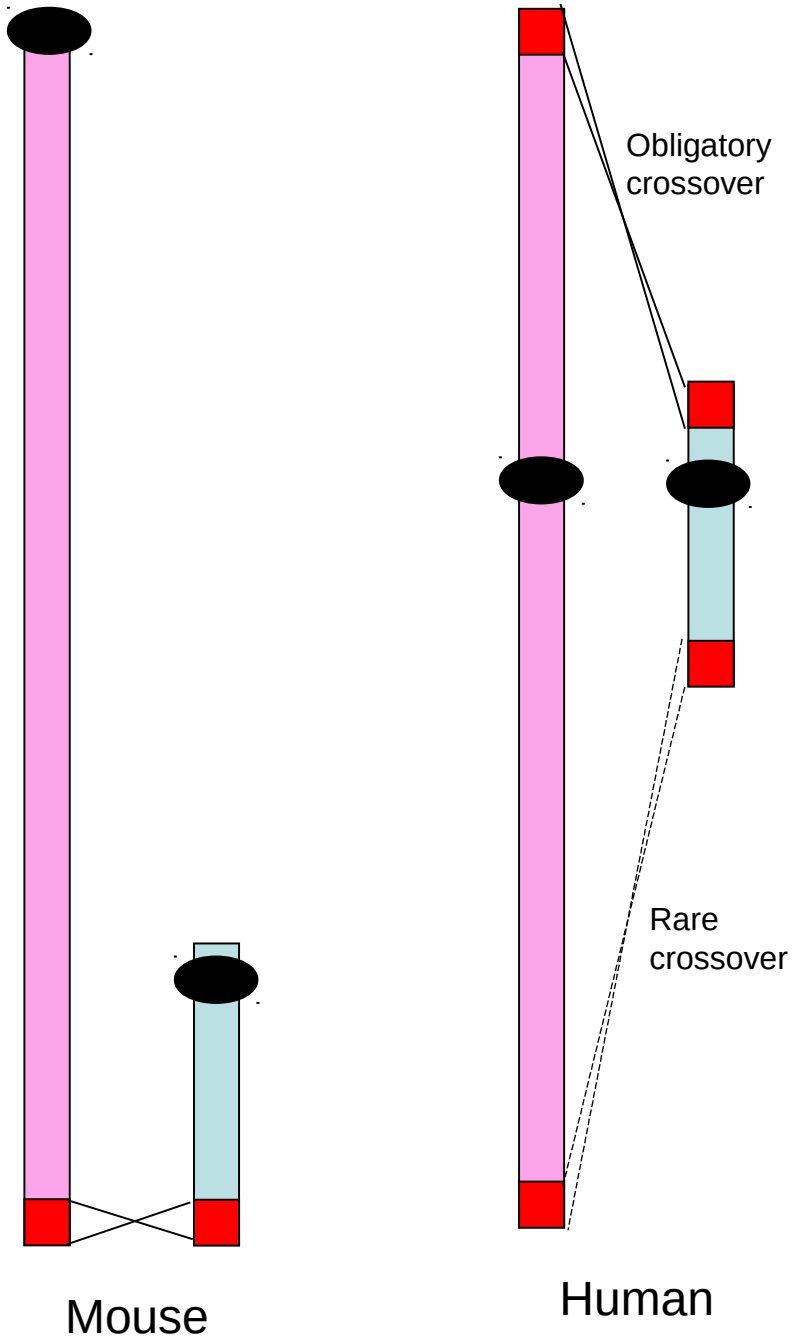


Explaining X chromosome conservation

Although addition through the PAR is a key mechanism affecting sex chromosome gene content, this sort of rearrangement is still very rare compared to autosomal translocations.

There have been four major chromosome segments added to the sex chromosomes in the course of human evolution (five strata = ancestral X plus four additions).

Rearrangements involving the autosomes are far more common.

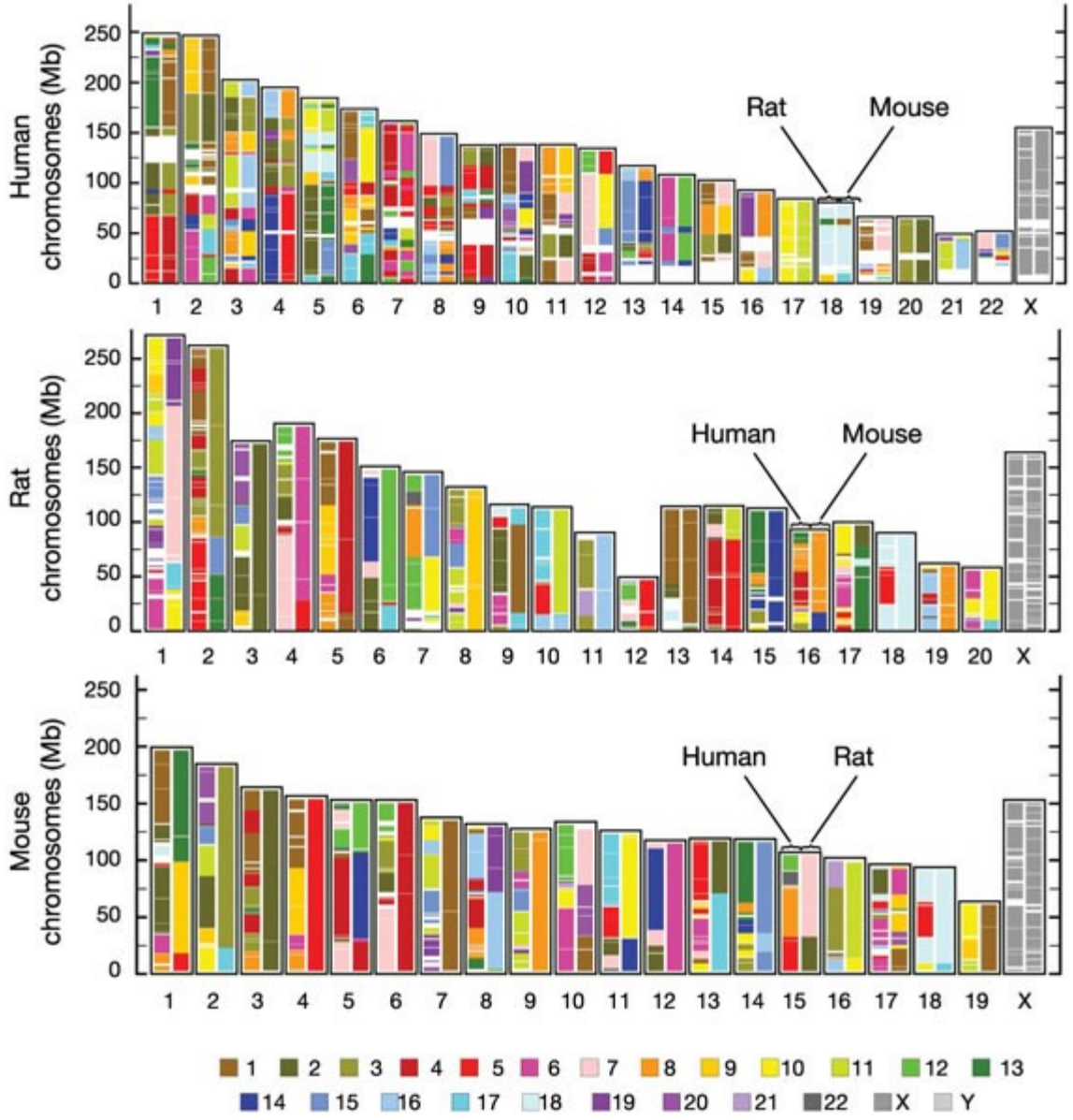


Figure 4 from Nature, volume 428, 493-521. *Genome sequence of the Brown Norway rat yields insights into mammalian evolution*

Explaining X chromosome conservation

Sex chromosome genes are faced with a dosage problem.
Y degeneration means the remaining X copy thus has to do “double duty”: achieved by upregulating the X gene or increasing its specific activity

i.e. compensation of the X:autosome ratio.

BUT! Compensated genes are now overexpressed in females.

Possible solutions:

* Increase expression from the single X in males (*occurs in Drosophila*)
* Halve the expression from both X’s in females (*occurs in C. elegans*)
* Inactivate one of the X’s in females (*occurs in mammals*)
  - random X inactivation (*placental mammals*)
  - imprinted X inactivation (*marsupials and extraembryonic tissues of placental mammals*)
* Control gene dosage on a gene-by-gene basis with no global dosage compensation (*occurs in birds*)

C. elegans downregulates both X's in females

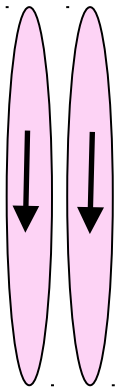
Drosophila upregulates the single X in males

Marsupials inactivate (imprint) the entire paternal X in females

Placental mammals inactivate Xp or Xm at random in females. EET follows marsupial pattern with imprinted Xp.

♀

Xp Xm



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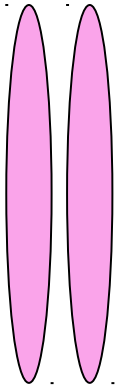

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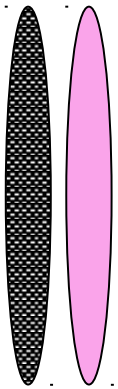

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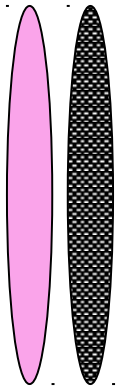

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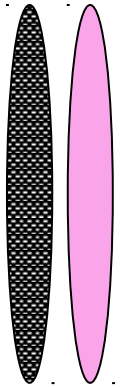

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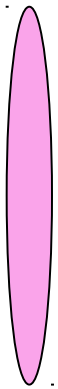
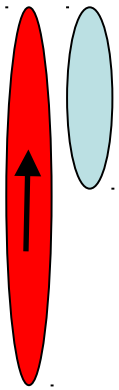


XO



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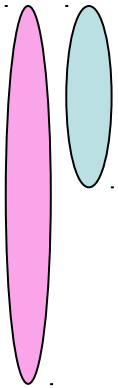

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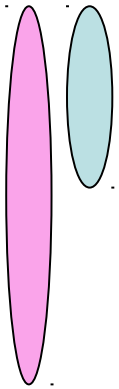


XY

Explaining X chromosome conservation

Once dosage compensation is established on the X chromosome, sequences from other chromosomes will find it hard to introgress directly onto the X as this would affect their dosage adversely. Thus the bulk of the X chromosome is highly conserved across all mammals.

X inactivation also appears to be at least partly responsible for the unusual repeat composition of the X chromosome (enrichment for LINE repeats).

- X inactivation spreads outwards from the X inactivation centre (Xic)
- When autosomal material is translocated to the X, inactivation spreads into the translocated chromatin and silences the genes involved
- Spreading of inactivation appears to be facilitated by the presence of LINE repeat elements, particularly full-length LINEs

- *Do these LINE elements act as "relay stations" for the spreading?*

Not all X genes are subject to X inactivation

The main exception is the PAR - pseudoautosomal region(s) that are identical between X & Y which are necessary for pairing at meiosis.

- PAR genes are present on both the X and Y, and are not subject to dosage compensation.
- Autosomal sequence can be recruited to the PAR without dosage complications arising.
- From the PAR, it may then become incorporated into the non-recombining region of the sex chromosomes, to be followed by attrition of the Y copy and preservation / dosage compensation of the X copies

Not all X genes are subject to X inactivation

A second class of exceptions are housekeeping genes retained on the Y. If the Y copies of the genes retain function, then there is no need for dosage compensation on the X. Therefore, such genes typically escape X inactivation.

A final class of exceptions in humans are genes on chromosome arm Xp. The Xic is on Xq, and spreading of inactivation through the centromere appears to be incomplete. This may also relate to the fact that Xp is the most recent addition to the X, and may not have finished the compensation process yet. More research in non-eutherian species would help to resolve this.

Lecture 1: Structural considerations

- Definition of sex chromosomes
  - Sex determining genes as a “switch” within a network
- X / Y heteromorphism: gross differences between X and Y
  - Reasons for Y degeneration
  - Reasons for X conservation
- Consequences of X / Y heteromorphism: dosage compensation
- Pathologies involving gross sex chromosomal abnormality
  - Aneuploidies
  - Defects involving X inactivation

Gross chromosomal anomalies and pathology

1. Chromosome Aberrations = mutations of the genetic material that involve large segments of a chromosome; consequently they can affect large numbers of genes.

2. They are very common; they affect 7.5% of all conceptions, most of which abort spontaneously. They are found in 0.6% of live births.

3. There are two groups of chromosome aberration.
   (a) Numerical abnormalities where there are abnormal numbers of chromosomes.
   (b) Structural abnormalities where there are structurally altered chromosomes.

4. These abnormalities can arise either in the germ line (and therefore will be found in all somatic cells) or in somatic lineages (and thus found in some somatic cells) leading to mosaics. Mosaicism can also arise through “rescue” of a germ line abnormality – e.g. nondisjunction at mitosis leading to elimination of an extra chromosome.

Gross chromosomal anomalies and pathology

- Polyploidy: extra *sets* of chromosomes
  e.g. triploidy with 69 chromosomes
  Caused by:
  - *Fertilisation with two sperm*
  - *Meiotic failures in sperm or ovum leading to diploid gametes*

- Aneuploidy: abnormal *number* of chromosomes
  Autosomal e.g. trisomy 21
  Sex chromosomal e.g. 45,X (Turner) 47,XXY (Kleinfelter)
  Caused by non-disjunction during meiotic or mitotic divisions

- Structural Abnormalities:
  Translocations; Inversions; Deletions; Duplications
  Caused by:
  - *chromosome breakage and joining of inappropriate ends (rate increased by mutagens, ionising radiation and X-rays)*
  - *Accidental recombination events between non-homologous chromosomes during meiosis*

TRIPLOIDY

- Usually 69,XXX or 69,XXY. 69, XYY much rarer, may be lost before detection?
- 2% of all conceptions, always miscarry
- Very poor growth, especially trunk
- Abnormal appearance (e.g. webbing of fingers)
- Multiple structural abnormalities
- Can appear as hydatidiform mole due to presence of two paternal genomes

Shows that *absolute* gene dosage matters as well as imbalance between different genes

ANEUPLOIDY

- Genetic imbalance of a whole chromosome or chromosomes
  - Trisomy (e.g. Down's syndrome, Kleinfelter syndrome)
  - Monosomy (e.g. Turner Syndrome)

- Usually embryonic lethal. The only aneuploidies to survive to term are those of the smaller chromosomes where fewer genes are affected (e.g. chromosome 21 in Down's syndrome), or of the sex chromosomes.

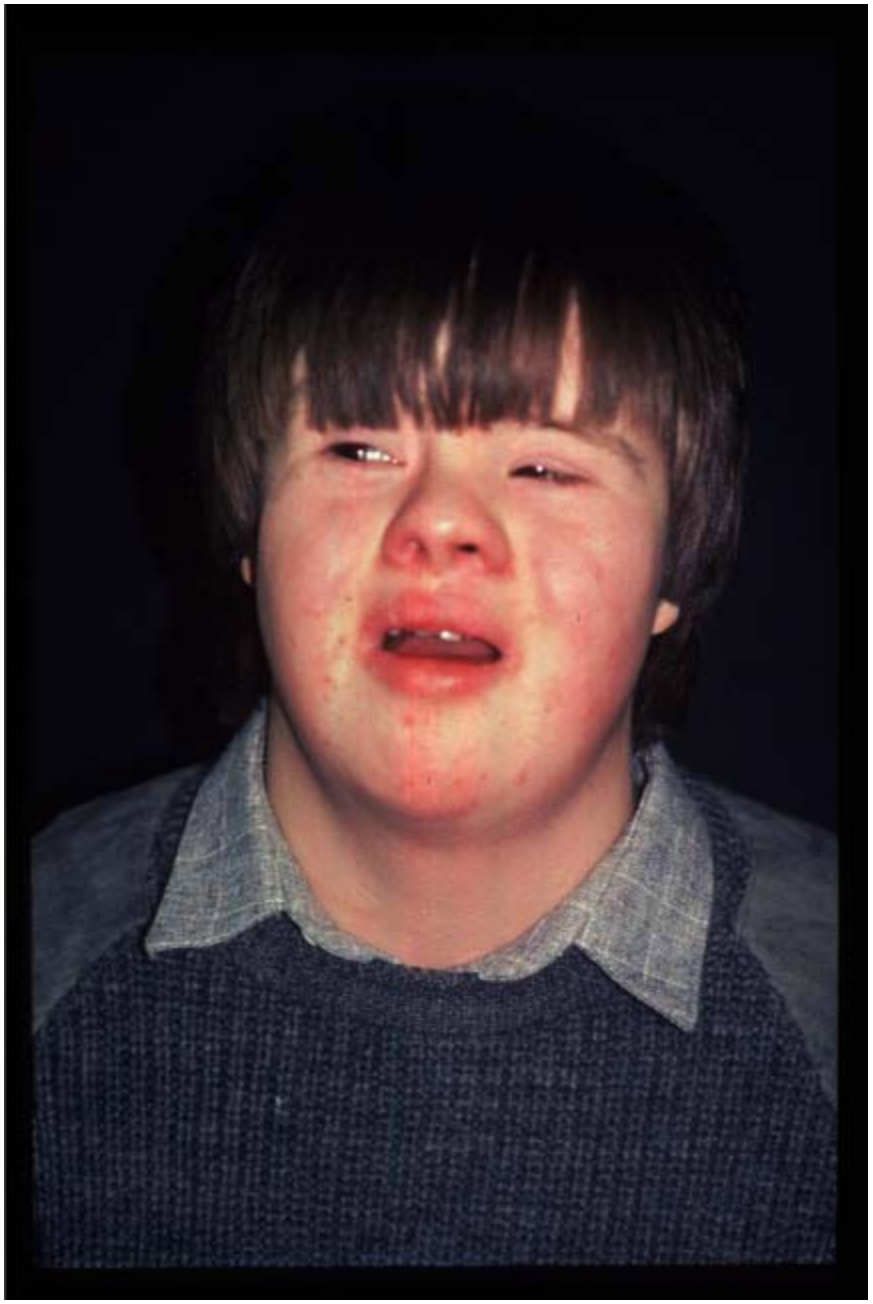
ANEUPLOIDY

Genetic Imbalance of
whole chromosomes.

e.g. **Trisomy 21, Down's Syndrome**

- Moderate mental retardation and developmental delay
- Characteristic facies including epicanthic folds
- Single palmar crease
- Large tongue
- Short limbs
- Poor muscle tone
- Risk of heart abnormalities
- Risk of middle ear abnormality

Smallest chromosome in the karyotype yet still has very widespread effects



SEX CHROMOSOME ANEUPLOIDY

- Less severe than autosomal aneuploidy despite the fact that the X is a comparatively large chromosome

- Extra copies of the X chromosome are inactivated

- Phenotype arises due to the fact that inactivation is incomplete: the pseudoautosomal region of the sex chromosomes is not inactivated, and some X-linked genes also escape inactivation.
    - *X-Y homologous genes where the Y copy has been retained*
    - *Genes on chromosome arm Xp*

- Monosomy X (Turner's syndrome) is more severe than excess sex chromosomes

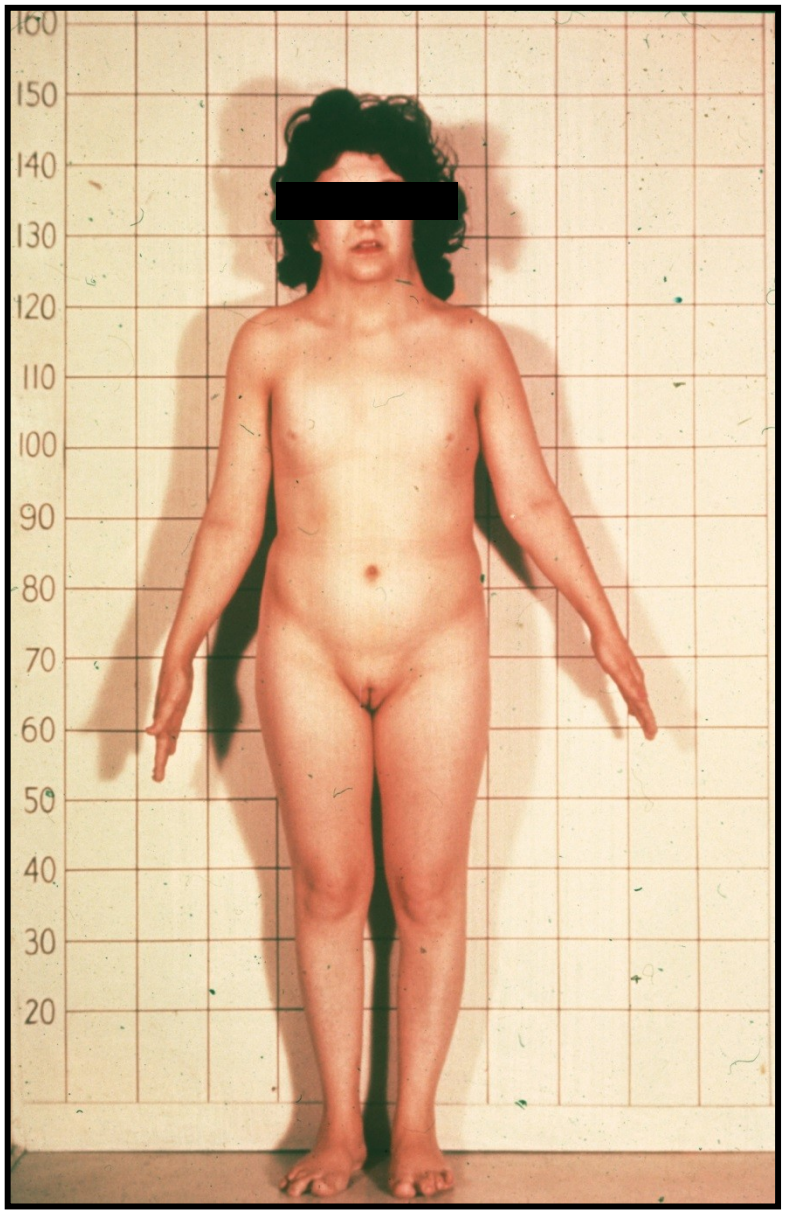
Turner Syndrome - 45,X0 – monosomy X

Gonadal anomalies:

- streak gonads through early degeneration of the ovary - infertile

Somatic anomalies:

- short stature
- skeletal anomalies e.g. wide carrying angle
- poor lymphatic system development (lymphatic hypoplasia). Leads to oedema during development and consequent webbing of the neck. Puffy feet in new-born
- Heart defects. Coarctation of the aorta
- Horse-shoe kidney
- Poor secondary sexual differentiation



47, XXY KLINEFELTER SYNDROME

- Male, normal newborn appearance
- Usually undiagnosed in children
- 10-20 point reduction in average IQ
- Long limbs, small testes
- Poorly developed adult sexual characteristics
- Diagnosed when adults investigated for infertility

47, XXX

- Female, normal appearance
- Usually undiagnosed
- Modest reduction in average IQ,
  mild mental handicap in 15-25% of cases

47, XYY

- Male, normal appearance
- Usually undiagnosed
- 10-15 point reduction in average IQ
- Tall stature
- Increased frequency of behavioural problems, particularly aggressive behaviour. Ascertainment bias?

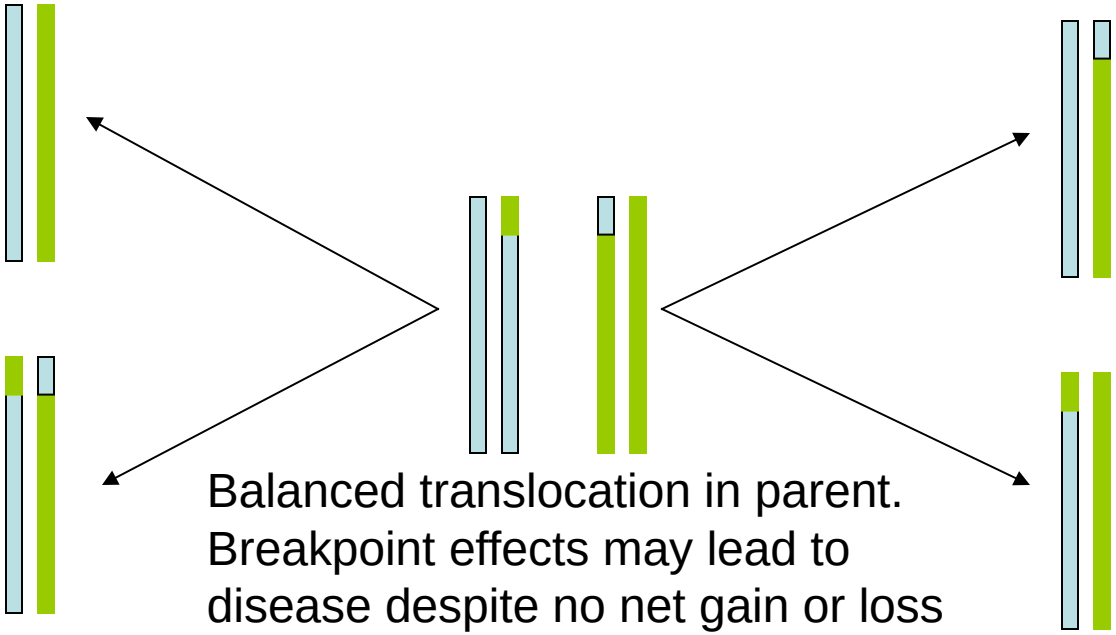
- Least effect of any aneuploidy even though extra Ys are not subject to inactivation, due to low gene content of the Y

STRUCTURAL ABNORMALITIES

Can cause disease either by

- altering gene content
  (i.e. duplication, deletion, unbalanced translocations)
- disruption of genes at chromosomal breakpoints
- fertility problems – pairing, balanced / unbalanced translocations

Only 50% of potential gametes contain a balanced gene complement: potential for recurrent miscarriage

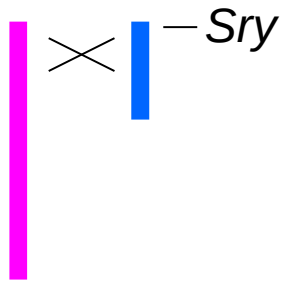


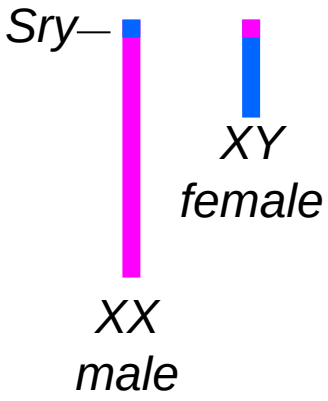
The other 50% of gametes are unbalanced and lead to duplication / deletion in the next generation

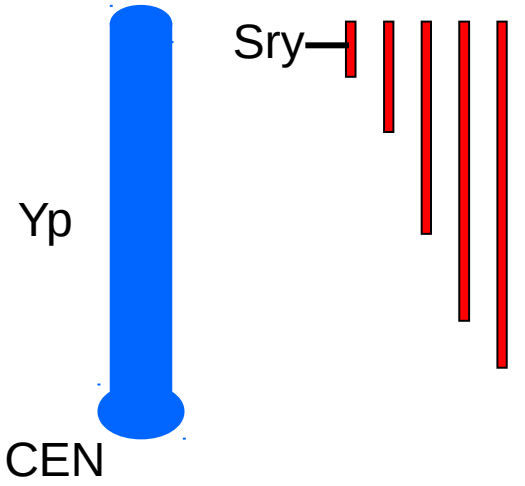
Balanced translocation in parent. Breakpoint effects may lead to disease despite no net gain or loss of DNA. Pairing issues may lead to meiotic arrest.

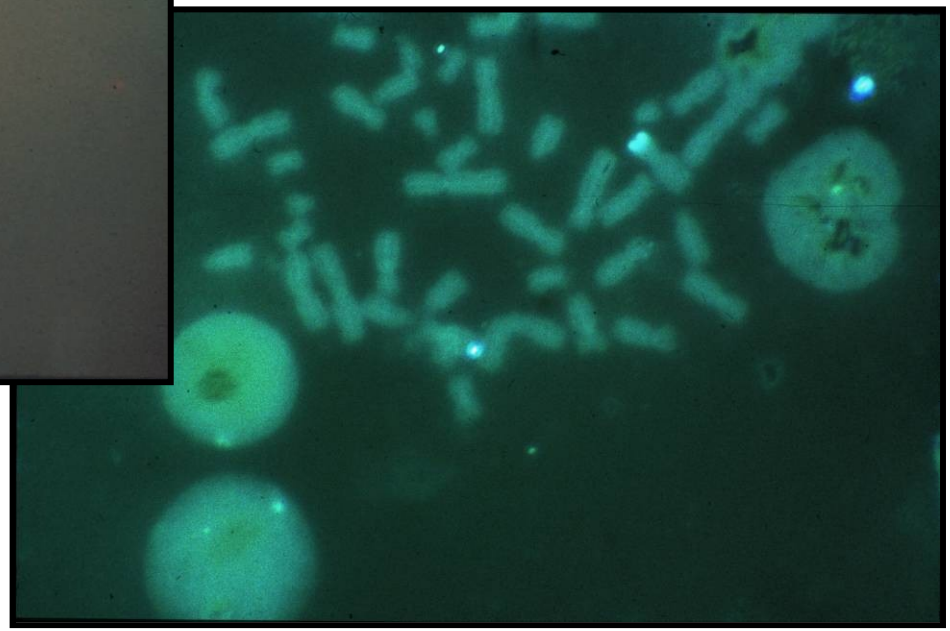
STRUCTURAL ABNORMALITIES

- Dosage effects
  e.g. sex reversal







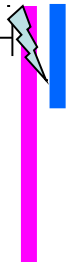


STRUCTURAL ABNORMALITIES

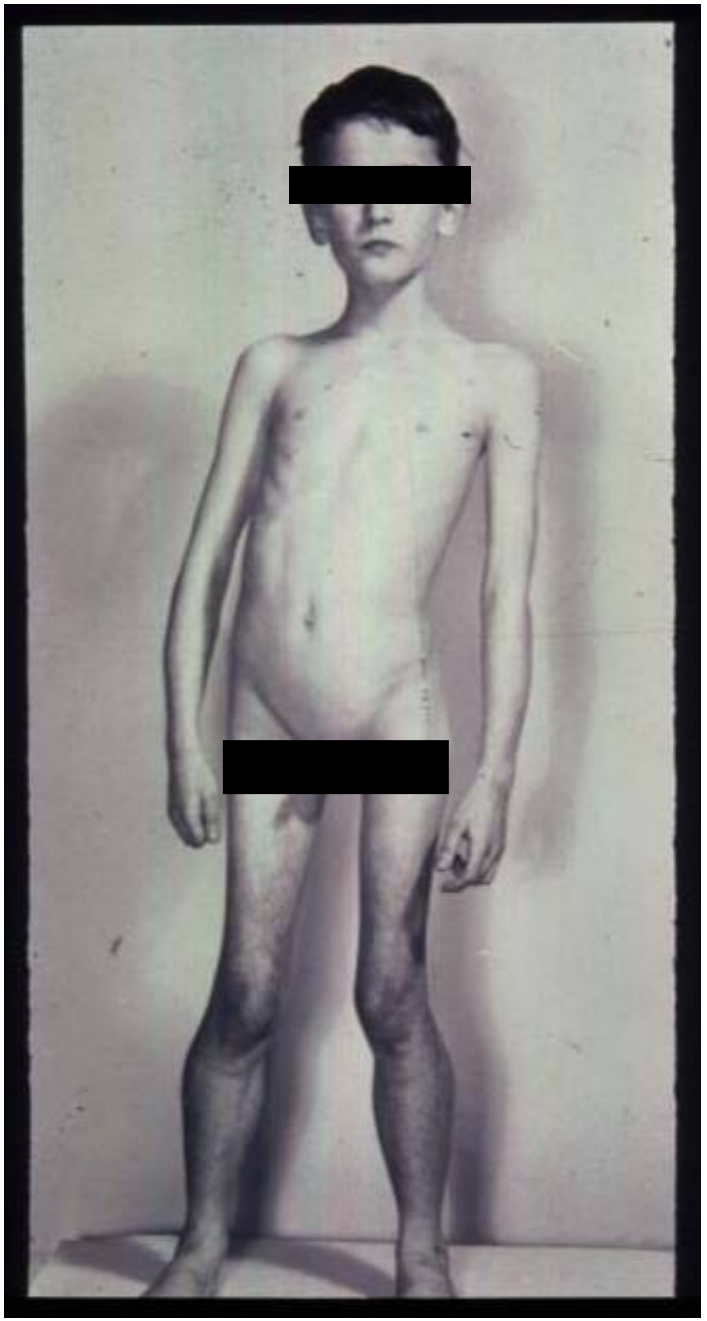
- Breakpoint effects
  e.g. Duchenne muscular dystrophy

Dystrophin

Mutation disrupts gene



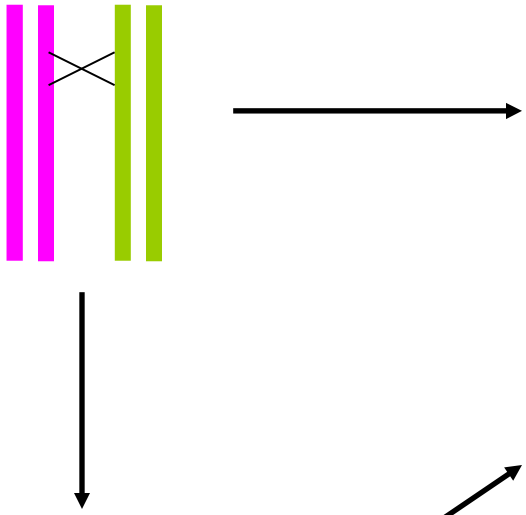
Females retain a normal X and are usually asymptomatic carriers

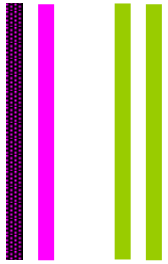


X INACTIVATION – SPREADING EFFECTS IN TRANSLOCATED CHROMOSOMES

- Inactivation of autosomal genes, potential skewing of inactivation

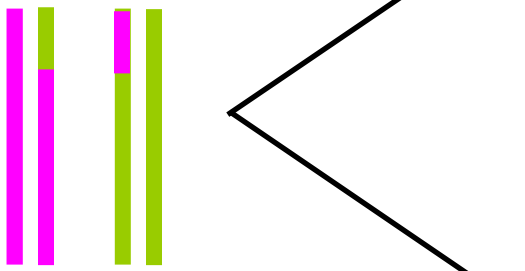
Normal female: two copies of each chromosome including X

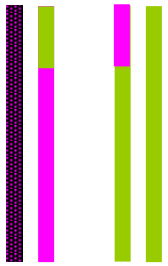




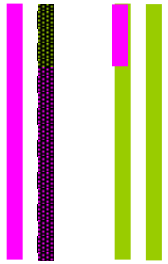
One X copy is inactivated (random choice)

X : Autosome translocation places autosomal genes in the context of X chromatin





Normal X copy inactivated: can uncover breakpoint effects in a female

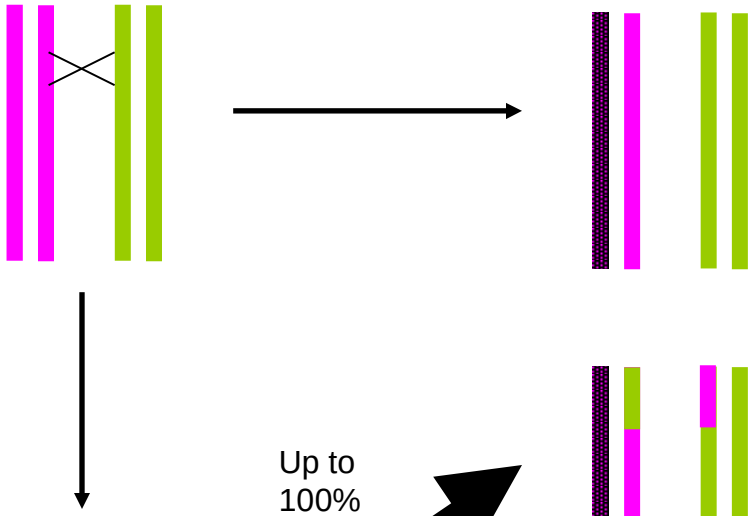


Derived X copy inactivated: functional monosomy for an autosomal segment, and duplication of an X segment. Often cell lethal

X INACTIVATION – SPREADING EFFECTS IN TRANSLOCATED CHROMOSOMES

- Inactivation of autosomal genes, potential skewing of inactivation

Normal female: two copies of each chromosome including X



One X copy is inactivated (random choice)

X : Autosome translocation places autosomal genes in the context of X chromatin

Up to 100% skew

Normal X copy inactivated: can uncover breakpoint effects in a female

Derived X copy inactivated: functional monosomy for an autosomal segment, and duplication of an X segment. Often cell lethal

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  - Aneuploidies
  - Rearrangements and translocations

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